I.10 Prednisolone, sumatriptan and verapamil – EML

Reviewer summary	☒ Supportive of the proposal ☐ Not supportive of the proposal Justification (based on considerations of the dimensions described below): This Application refers to the inclusion of - sumatriptan subcutaneous injection: 6 mg/0.5 mL pre-filled syringe or autoinjector - verapamil tablet Immediate-release tablets: 40 mg, 80 mg, 120 mg and extended-release tablets: 120 mg, 180 mg, 240 mg - prednisolone oral tablets: 5 mg, 25 mg for the treatment of **cluster headache** in adults on the Model List of Essential Medicines List (EML). The EML has no dedicated section to cluster headache, therefore no other medicines are currently listed for this condition. Sumatriptan, verapamil, prednisolone are already listed for different disorders. Cluster headaches are the most common of the primary headache types known as trigeminal autonomic cephalgias. They are relatively rare, occurring in 0.1% of the general population. Typical age of onset is approximately 30 years and men are three times more likely to suffer from this condition than women, though current research has shown that the ratio has decreased over time. Oxygen treatment and triptans, i.e. subcutaneous sumatriptan, are the recommended treatment for acute attacks, while verapamil is the most widely prescribed medication for prophylaxis. Glucocorticoids are also recommended as preventive therapy for people with episodic cluster headaches and active cluster periods that are infrequent and last less than two months. Ref: https://www.ncbi.nlm.nih.gov/books/NBK544241/ **SUMATRIPTAN** The evidence presented in the application supports the efficacy of subcutaneous sumatriptan for the acute management of cluster headache attacks, offering rapid symptom relief. Adverse events were more common with a triptan than with placebo, but they were generally of mild to moderate severity. Ref: https://doi.org/10.1002%2F14651858.CD008042.pub3. A network meta-analysis suggests that sumatriptan injectable is more likely to be effective when compared to zolmitriptan nasal spray, octreotide, and non-invasive vagal nerve stimulation. Ref: https://doi.org/10.1111/head.14283 The cost analysis reported in the Application showed that sumatriptan 6 mg subcutaneously is not cost-effective. Data on costs are however sparse, and the reliability of this analysis is limited. In Prices of subcutaneous injection is similar to that of nasal spray in some countries and roughly twice tin others. Oral formulations are less costly; however, they are not recommended for this condition due to the slow onset of action. Accessibility and availability do not present major issues. Based on these considerations, this Reviewer supports the inclusion of subcutaneous sumatriptan for the acute management of cluster headache attacks. Costs may be an obstacle to coverage in some countries, therefore generics use should be encouraged. The role of inhaled oxygen can also be discussed by the Committee. **VERAPAMIL** People with chronic cluster headache often require preventive therapy. The rationale for using verapamil as a first-line preventive treatment is based on a limited evidence base, i.e. two small randomized controlled trials (RCTs) and three observational studies. Pooled indicated that 87% of patients reached either a complete response or a more than 50% reduction in attack frequency with verapamil. Typical dosing for verapamil begins at 80 mg three to four times daily, with gradual increases.

	Costs, accessibility and availability do not present major issues. Based on these considerations, this Reviewer supports the inclusion of verapamil for the prevention of cluster headache attacks, although the evidence supporting its efficacy is limited. It is important to stress the need for ECG monitoring due to potential cardiac side effects. **PREDNISOLONE/PREDNISONE** Corticosteroids may be used for short-term bridging therapy during the initiation or adjustment of preventive treatments. The most robust evidence reported in the application refers to prednisone 100 mg as fast-acting, short-term preventive treatment for episodic cluster headache that can be used to attenuate the early cluster episode until long-term prevention has reached its full efficacy. Prednisolone/prednisone costs, accessibility and availability do not present major issues. Based on these considerations, this Reviewer supports the inclusion of prednisolone for bridging preventive therapy of cluster headache. The Committee may consider listing prednisone – the prednisolone biologically inactive (prodrug) - as the alternative, consistently with existing listings in other indications.
Does the EML and/or EMLc currently recommend alternative medicines for the proposed indication that can be considered therapeutic alternatives? (**https://list.essentialmeds.org/**)	☐ Yes ☒ No ☐ Not applicable
Does adequate evidence exist for the efficacy/effectiveness of the medicine for the proposed indication? **SUMATRIPTAN** A Cochrane review showed that triptans were more effective than placebo for headache relief and pain-free responses. With subcutaneous sumatriptan 6 mg, 48% of participants were pain-free and 75% had no pain or mild pain (17% and 32% respectively with placebo). Number needed to treat for subcutaneous sumatriptan was 3.3 (95% CI 2.4 to 5.0) and 2.4 (1.9 to 3.2) respectively (low certainty of evidence, 2 studies). Ref: https://doi.org/10.1002/14651858.CD008042.pub3 A more recent network meta-analysis including a total of 13 randomized controlled trials found that high flow oxygen is the most effective therapy for headache response at 15 and 30 min (OR 9.0, 95% CrI 5.3 to 15.9 vs. placebo), with injectable sumatriptan demonstrating the next highest effect (OR 6.4, 95% CrI 3.75 to 11.1 vs. placebo). Certainty of evidence not assessed. One study out of three judged at low risk of bias Ref: https://doi.org/10.1111/head.14283 **VERAPAMIL** Two randomised trials have investigated the prophylactic effect of verapamil in cluster headache. One small (N=30) double-blind randomised placebo-controlled trial showed that verapamil 360 mg decreased daily attack frequency vs placebo (0.66 ± 0.88 vs. 1.65 ± 1.01, respectively) and daily analgesic use (0.5 ± 0.87 vs. 1.2 ± 1.03, respectively). In the second week, 80% on verapamil reported 50% or higher reduction in attack frequency compared with 0% on placebo, however, just 27% became attack free. A double-blind cross-over RCT lasted 23 weeks comparing verapamil 360 mg/day with lithium 900 mg/day in CCH (no placebo group). Only 50% on verapamil and 37% on lithium experienced a reduction in an unspecified headache index. Ref: https://doi.org/10.1186/s10194-023-01660-8 A pooled analysis of non-comparative observational studies showed that 73% of the patients (95%CI 0.59-0.84) who received verapamil reached either a complete response or a 50% or more reduction in the attack frequency.	☒ Yes ☐ No ☐ Not applicable

PREDNISOLONE/PREDNISONE The Application reported data from a multicentre, publicly-funded, randomised, double-blind, placebo-controlled trial done in ten specialised headache centres in Germany (Ref https://doi.org/10.1016/ S1474-4422(20)30363-X). 118 participants between 18 and 65 years with episodic cluster headache and within a current pain episode for not more than 30 days, received 100 mg oral prednisone for 5 days followed by tapering of 20 mg every 3 days, or matching placebo. Participants in the prednisone group had a mean of 7.1 (SD 6.5) attacks within the first week compared with 9.5 (6.0) attacks in the placebo group (difference –2.4 attacks, 95% CI –4.8 to –0.03). Two older studies from 1978 and 1975 also indicated some efficacy of prednisone. The evidence is about prednisone, prednisolone prodrug. The main difference between prednisone and prednisolone is that prednisone must be converted by liver enzymes to prednisolone before it can work. They are used to treat similar conditions and are generally considered equally effective and safe. In people with reduced hepatic function, prednisolone is usually preferred.	
Does adequate evidence exist for the safety/harms associated with the proposed medicine? **SUMATRIPTAN** Sumatriptan is contraindicated in people with a history of ischemic heart disease, uncontrolled hypertension, or cerebrovascular disease because of its vasoconstriction, which can lead to coronary artery vasospasm, myocardial infarction, or stroke. **VERAPAMIL** Verapamil can lead to heart block, and slow tapering is strictly recommended to avoid cardiac complications. Adverse events such as constipation and edema can be dose limiting. In rare cases, verapamil can lead to severe skin reactions. **PREDNISOLONE/PREDNISONE** Similar rate of adverse events was observed in the German study: in the prednisone group, 37 (71%) of 52 patients reported 135 adverse events (most common were headache, palpitations, dizziness, and nausea) and in the placebo group, 39 (71%) of 55 patients had 135 adverse events (most common were nausea, dizziness, and headache). Safety profile of prednisolone is well-known, as well as that of other corticosteroids. Prednisolone is not suitable for long-term use due to its associated side effects.	☒ Yes ☐ No ☐ Not applicable
Overall, does the proposed medicine have a favourable and meaningful balance of benefits to harms?	☒ Yes ☐ No ☐ Not applicable
Are there any special requirements for the safe, effective and appropriate use of the medicines? **SUMATRIPTAN** Cardiovascular risk assessment and clinical monitoring during use. **VERAPAMIL** Baseline and periodic ECG monitoring to detect potential cardiac issues such as bradycardia or heart block **PREDNISOLONE/PREDNISONE** Monitoring for corticosteroid-related side effects, including hyperglycemia and hypertension	☒ Yes ☐ No ☐ Not applicable
Are there any issues regarding price, cost-effectiveness and budget implications in different settings? **SUMATRIPTAN**	☒ Yes ☐ No ☐ Not applicable

The cost analysis reported in the Application showed that sumatriptan 6 mg subcutaneously is not cost-effective. Data on costs are however sparse, and the reliability of this analysis is limited. In Prices of subcutaneous injection is similar to that of nasal spray in some countries and roughly twice tin others. Oral formulations are less costly; however, they are not recommended for this condition due to the slow onset of action. **VERAPAMIL and PREDNISOLONE/PREDNISONE** No issues	
Is the medicine available and accessible across countries?	☒ Yes ☐ No ☐ Not applicable
Does the medicine have wide regulatory approval?	☒ Yes, for the proposed indication ☐ Yes, but only for other indications (off-label for proposed indication) ☐ No ☐ Not applicable